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MICHAEL P. MORRIS
BOEHRINGER INGELHEIM CORPORATION
900 RIDGEBURY ROAD
P. O. BOX 368
RIDGEFIELD, CT 06877-0368

EXAMINER	
OLSON, ERIC	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 07/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/614,365	MEADE ET AL.	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/22/03, 9/19/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

This application claims benefit of provisional application 60/407895, filed September 3, 2002 and foreign application DE10230769.5, filed July 9, 2002. Claims 1-43 are pending in this application and examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims recite a number of chemical names, including Bay-198004, CP-325366, BY343, D-4396, V-11294A, and AWD-12-281. These names are not standard chemical or trivial names and do not clearly and definitely identify which compounds are indicated, thereby rendering the claims indefinite.

Claim 6 contains the trademark/trade name Ariflo®. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of

goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe a particular pharmaceutical compound and, accordingly, the identification/description is indefinite.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 and 8-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition comprising an anticholinergic of formula 1 and a specific PDE-IV inhibitor described in the art to be useful for the treatment of obstructive pulmonary disease, such as theophylline or cliomilast (Ariflo®), does not reasonably provide enablement for a combination of **1** with any PDE-IV inhibitor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims;

(6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is a pharmaceutical composition comprising two pharmaceutical compounds, one being an anticholinergic agent of formula **1**, and the other being a PDE-IV inhibitor, or else an inhaler to be used in the delivery of such a composition, or a method of using the composition to treat an inflammatory or obstructive disease of the respiratory tract. Note that merely possessing two compounds does not enable one skilled in the art to produce a pharmaceutical composition comprising the two compounds in the absence of a motivation to combine them, such as the reasonable expectation that both compounds will be useful for treating the same condition and will produce at least an additive effect when administered together.

The state of the prior art: The anticholinergic agent **1** is known to be useful for the treatment of obstructive pulmonary diseases. A number of selective PDE-IV inhibitors are also known to be useful for the same purpose, for example a number compounds of formula **2a,** or pharmaceuticals such as enprofylline or roflumilast. According to PCT international publication WO03/011274 (reference included with PTO-1449) the human PDE-4 enzyme exists in at least two distinct forms possessing different biological activity. Thus different PDE-4 inhibitors are expected to possess different biological activities depending on their relative affinities for the different forms of PDE-IV.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: As there exist more than one form of the PDE-4 enzyme, there similarly exist more than one type of PDE-4 inhibitor. Thus PDE-4 inhibitors are expected to possess differing activities, and to be individually more or less suitable for the treatment of obstructive pulmonary disease.

Furthermore, synergistic effects and other drug-drug interactions are not expected to be uniformly consistent across all combinations of **1** with any PDE-4 inhibitor. Avery's Drug Therapy, 3rd edition, states that, "Pharmacokinetic interactions observed *in vitro* or in animals will not necessarily occur in man," "Interactions will not necessarily occur in all patients receiving a given combination of drugs known to have a potential for interaction in man," and "Many clinically important interactions, especially those of a pharmacokinetic nature, depend on a variety of factors additional to the drugs given." (Chapter VIII, p. 255, Synopsis of Important Principles, no. 4-6) Although the cited text deals primarily with adverse drug-drug interactions, beneficial drug-drug interactions function in a similar manner according to similar mechanisms. Thus the determination of every possible interaction between two broad classes of drugs is expected to be highly unpredictable, especially when one of the drugs being combined has properties which are unpredictable to begin with.

The Breadth of the claims: The term PDE-IV inhibitor as it appears in claim 1 is interpreted to mean any compound capable of inhibiting any form of PDE-4. This includes compounds which are not selective for one subtype of PDE-4 over the other, as well as those which possess significant activity against other phosphodiesterase enzymes.

The amount of direction or guidance presented: No direction or guidance is provided to inform one skilled in the art as to the full extent of compounds which are PDE-4 inhibitors, or to the extent of PDE-4 inhibitors which are useful in the claimed invention. No general guidelines are given for the discovery of novel PDE-4 inhibitors or for predicting their subtype selectivity or other interactions with 1. A number of PDE-4 inhibitors are described as preferred embodiments of the invention but they are not limiting.

The presence or absence of working examples: No working examples are presented of the actual therapeutic efficacy of any of the claimed combinations.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as drug-drug interactions of novel compounds. See MPEP 2164.

The quantity of experimentation necessary: According to the Chemical Abstracts Service 2006 catalog, the Chemical Abstracts Registry contains entries for approximately 26 million organic and inorganic substances, all of which are potentially involved in the claimed method if they happen to possess allosteric MMP-13 inhibitory activity. The Sigma-Aldrich Rare Chemical Library contains over 80000 compounds, all of which are commercially available and also potential candidates for use in the claimed invention. The total number of compounds known either (a) to be PDE-4 inhibitors or (b) to not be PDE-4 inhibitors is merely an insignificant fraction of the total number of compounds whose PDE-4 inhibitory activity or lack thereof is not known. The existing literature does not identify any general method by which allosteric inhibitors of PDE-4

can be identified across all classes of molecular entities claimed other than by synthesizing and testing each one. In order to practice the invention with the full range of PDE-4 inhibitors beyond the limited number disclosed in the specification, one skilled in the art would be required to undertake a full-scale, high-throughput drug discovery program to discover the additional PDE-4 inhibitors not specifically recited in the specification.

In the process of screening the extensive number of compounds required to practice the claimed invention, one would be forced to synthesize said molecules. As no synthetic procedures are described and no references cited that teach synthetic protocols to synthesize PDE-4 inhibitors, or potential lead compounds which may be PDE-4 inhibitors, other than the admittedly incomplete list of examples, one wishing to practice the invention would be forced to design novel synthetic pathways. Since synthesis of organic small molecules is complex, the entire scope of claimed molecules cannot be synthesized by simple variations on a core synthetic scheme. In fact, current knowledge of the field of organic synthesis is far from complete, as evidenced by the fact that many synthetic schemes are still considered to be sufficiently novel to be patented, as evidenced by US patents 6500954, 6500955, and 6500972, all of which relate to synthetic methods. Since no structural limitations are given to the claimed invention, the list of compounds to be synthesized would include an enormously diverse set of structures and require an equally diverse array of synthetic procedures to produce them. Thus one of skill in the art would be forced to invest a considerable amount of

time and effort devising chemical syntheses spanning all fields of organic, inorganic, and biological chemistry.

In addition to synthesizing candidate compounds and carrying out *in vitro* studies on the molecular target, one wishing to practice the therapeutic method of claims 5-9 would also be required to undertake *in vivo* tests in animal models of obstructive pulmonary disease in combination with 1 in order to determine the presence or absence of a synergistic effect. Animal experiments include, along with the actual induction of disease state, administration of the potential pharmaceutical compound, and collection and analysis of data, additional burdens associated with compliance with animal welfare regulations, care, feeding, and other maintenance of the animals, dissection of dead animals to collect data, and disposal of dead animals after the protocol is finished. Because of the unpredictability of the art and the lack of any generalized method for predicting the pharmacological properties of any arbitrarily chosen molecule, these animal experiments would need to be repeated thousands of times, and involve the maintenance, killing, and disposal of at tens of thousands of experimental animals at minimum, to establish the suitability or lack thereof for each compound found to possess the desired activity *in vitro*.

The sort of industrial-scale interdisciplinary drug discovery program described in the preceding paragraphs would present an undue amount of experimentation to require of anyone wishing to practice the invention.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent

protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the broad scope of the claims and the lack of guidance from Applicant's disclosure, Applicants fail to provide information sufficient to practice the claimed invention for all possible PDE-4 inhibitors.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Knowles et al. (PCT international publication WO03/011274, reference included with PTO-1449) in view of Meissner et al. (US patent 6706726, cited in PTO-1449) further in view of Hill et al. (US patent 6060069, reference cited in PTO-892) Knowles et al. discloses combinations of an anticholinergic and a PDE-4 inhibitor and methods for their use in preventing or reducing the symptoms of pulmonary disease. (p. 1, lines 1-7) Theophylline is mentioned as an example of a PDE-4 inhibitor. (p. 3, lines 25-26) Cilomilast (Ariflo®, as recited in instant claims 6-7) is mentioned as a particularly preferred PDE-4 inhibitor. (p. 4, lines 13-14) An example is provided of a pharmaceutical dose formulation which comprises a 1:1 ratio of cliomilast and tiotropium

bromide, an anticholinergic, in 18 μg each in a metered dose inhaler with 1,1,1,2-tetrafluoroethane, also known as TG134a, (p. 10, table 1, lines 4-9) falling within the limitations of instant claims 8-13 and 19-22 for use in an inhaler according to instant claim 40. Another embodiment is a powder formulation for a dry powder inhaler comprising cliomilast and tiotropium bromide mixed with lactose as an excipient, (p. 10, lines 10-19) in the limitations of instant claims 11-14, enclosed in a hard gelatin capsule and enclosed in an inhaler according to instant clams 14, 17 and 40. Knowles et al. does not disclose a pharmaceutical combination comprising **1** and a PDE-4 inhibitor. Knowles et al. also does not disclose an inhalable powder having a particle size of up to 250μm or between 10 and 150μm, as described in instant claims 15-16 or an inhalable powder comprising only **1** and **2** as described in instant claim 18, or a propellant containing inhalable aerosol containing additional ingredients according to instant claim 23, or a propellant-free inhalable solution according to instant claims 25-38.

Meissner et al. discloses anticholinergic compounds of a general formula which includes **1** as an embodiment. (Example 1, column 10, lines 10-29) These agents are expected to be useful in the treatment of chronic obstructive pulmonary disease and asthma. (column 19, lines 63-65) Meissner et al. specifically discloses that these compounds may be administered by inhalation. (column 22, lines 26-29) Specific formulations described by Meissner et al. include an aerosol spray for use in an inhaler, (column 24, lines 40-55) an inhalable solution according to instant claims 25-29, 32, 33, 36, and 39 for use in an inhaler according to instant claim 42, (column 24, lines 58-67)

and a powder comprising the active substance and lactose monohydrate. (column 25, lines 15-20)

Hill et al. discloses a method of treating pulmonary disease by administering a drug as an inhalable powder using lactose as an excipient, in which the lactose particles are in the size range of between 20 and 100 microns. (column 3, lines 38-46)

It would have been obvious to one of ordinary skill in the art at the time of the invention to produce a composition similar to those disclosed by Knowles et al. comprising the anticholinergic drug of Meissner et al. in place of the anticholinergics disclosed by Knowles et al and to use this combination in the therapeutic method of claim 43. It would also have been obvious to one of ordinary skill in the art to prepare this composition as an inhalable powder comprising the active ingredients and lactose with a particle size of between 20 and 100 microns as described by Hill et al, or an inhalable powder comprising only **1** and **2**. It would furthermore have also been obvious to prepare the pharmaceutical composition as a propellant-containing aerosol containing additional ingredients as described in claim 23, or as a solvent-free inhalable aerosol as described in claims 25-39.

One of ordinary skill in the art would have been motivated to prepare the composition using the anticholinergic compound **1** of Meissner et al. in place of the anticholinergics of Knowles et al. because this compound is also an anticholinergic, is structurally similar to the compounds of Knowles et al., and is useful for treating the same condition. (i.e. obstructive pulmonary disease) One of ordinary skill in the art would have been motivated to prepare the composition as an inhalable powder

One of ordinary skill in the art would have reasonably expected success in preparing the pharmaceutical composition with the compound of Meissner et al. because of the similarities between this compound and those already known to be useful in this invention. One of ordinary skill in the art would reasonably have expected success in preparing an inhalable powder with a particle diameter between 20 and 100 microns and an inhalable solution according to claims 25-29, 32, 33, and 36 because these formulations are taught in Meissner et al. and Hill et al. to be useful for pulmonary delivery of drugs. One of ordinary skill in the art would have been motivated to make various minor modifications such as adding ingredients as described by claims 23, 30, 31, 34, and 35 or subtracting them as described in instant claims 18, 36, and 37 because these modifications are minor modifications which are well within the routine skill of one of ordinary skill in the art.

Thus the invention taken as a whole is *prima facie* obvious.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-7, and 43 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of US patent application 10/613783 (Cited in PTO-1449, herein referred to as '783) in view of claims 1-8, 11, and 21-23 of U.S. Patent No. 6706726 (Meissner et al, cited in PTO-1449) Claims 1-10 of '783 et al. are drawn to combinations of an anticholinergic drug with a PDE-IV inhibitor. Claims 5 and 6 of Pairet et al. are drawn to such a composition in which the anticholinergic is a tiotropium, oxitropium, or ipratropium salt. These classes of anticholinergics share a substantial structural similarity with the claimed compound 1. Claims 9-10 of Pairet et al. disclose compositions comprising an anticholinergic and a PDE-IV inhibitor in which the PDE-IV inhibitor is one of the exact same inhibitors recited in instant claims 6-7. Claim 13 of Pairet et al. discloses a pharmaceutical composition of an anticholinergic drug and a PDE-IV inhibitor which is suitable for inhalation. Claims 1-13 of '783 et al. do not disclose a pharmaceutical combination comprising 1 and a PDE-4 inhibitor.

Claims 1-5 of Meissner et al. are drawn to anticholinergic compounds of a general formula which includes 1 as an embodiment. Claim 11 is drawn to the compound 1 itself. Claims 6-8 and 21-23 are drawn to methods of using this compound

in the treatment of conditions including chronic obstructive pulmonary disease and asthma.

It would have been obvious to one of ordinary skill in the art at the time of the invention to produce a composition similar to those disclosed by Pairet et al. comprising the anticholinergic drug of Meissner et al. in place of the anticholinergics disclosed by Pairet et al. and to use this combination in the therapeutic method of claim 43. One of ordinary skill in the art would have been motivated to prepare the composition using the anticholinergic compound **1** of Meissner et al. in combination with a PDE-4 inhibitor as described by Pairet et al. because the compounds in the compositions of Pairet et al. also contain anticholinergics which are structurally similar to compound **1**, and are useful for treating the same condition. (i.e. obstructive pulmonary disease) One of ordinary skill in the art would have reasonably expected success in preparing the pharmaceutical composition with the compound of Meissner et al. because of the similarities between this compound and those already known to be useful in this invention.

This is a provisional double patenting rejection because the conflicting claims have not yet been patented.

Conclusion

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Eric Olson
Patent Examiner
AU 1623
7/18/06

Anna Jiang
Supervisory Patent Examiner
AU 1623